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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,750	03/20/2002	Nobuhiko Nakashima	3190-015	8810

33432 7590 01/26/2005

KILYK & BOWERSOX, P.L.L.C.
53 A EAST LEE STREET
WARRENTON, VA 20186

EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,750	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-4,12,14,18,19,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-11,13,15-17 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/18/02 & 3/20/02* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d). It is noted, however, that applicant has not filed a certified copy of the Japan 2001-016746 application as required by 35 U.S.C. 119 (b).

Election/Restrictions

2. Applicant's election with traverse of Group II, claims 5-11, 13, 15-17 and 20-27, directed to a method for synthesizing a heterologous protein utilizing a polynucleotide comprising a base sequence having a RNA higher order structure in a cell-free system, and a nucleotide sequence of SEQ ID NO:1 in the response to the restriction requirement filed December 16, 2004 is acknowledged. The traversal is on the ground(s) that under the PCT rules, if there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features that define a contribution over the prior art, the unity of invention exists. The claimed inventions commonly relate to the RNA molecules that have a higher order structure having at least pseudoknot (PK) I, II and III structures can function to promote translation activity, regardless of whether a protein is synthesized in a cell or in cell-free system in the method claims; and it would not be serious burden for the Examiner to extend the search to include a method of protein synthesis using the same polynucleotide in a cell; regarding the selection of one sequence among the RNA sequences of SEQ ID NOs:1-7, since these RNA sequences share a common higher order structure (PK I, PK II and PK III) and four stem-loop structures, and have a common activity, thus the RNAs of SEQ ID NOs:1-7 are linked by a special technical feature to form a single inventive concept, and meet the requirement of unity of invention (pages 3-6 of the response). The response has been considered, however, the argument

is not fully persuasive because a method of synthesis of a heterologous protein (i.e., luciferase (LUC)) *in vitro* using an RNA of PSIV is known (Sasaki et al., J. Virology, 73, 1219-1226, (1999), especially page 1221, right column, last paragraph; Figs 5 and 7), thus, the special technical feature of the instant application is known and the claimed subject matter does not define a contribution which each of the claimed invention, considered as a whole, makes over the prior art. Regarding the burden of search, the search for each of the invention is not coextensive particularly with regard to the literature search. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other group. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exist. Regarding the selection of one RNA sequence from SEQ ID NOs: 1-7, the argument is persuasive, the restriction requirement of selection of one sequence is withdrawn. Therefore, claims 5-11, 13, 15-17 and 20-27, and SEQ ID NOs:1-7 are examined.

Informality

The disclosure is objected to because of the following informalities:

3. In the amendment filed July 18, 2002, SEQ ID NO:8 has been added to the primer sequence at line 2, page 18, however, this sequence having 20 nucleotides is not consistent with the sequence of SEQ ID NO:8 (19 nucleotides) in the sequence listing. Appropriate correction is required.

Sequence Listing

4. The paper copy of sequence listing filed May 14, 2003 is acknowledged, CRF has been entered.

Drawings

5. The proposed drawings of Figs. 3 and 8 filed July 18, 2002 is acknowledged. Please submit a complete set of formal drawings.

Claim Objections

6. Claims 5, 6, 10, 11, 13, 15 and 20-25 are objected to because the claim contains recitation of non-elected invention, protein synthesis in a cell.

7. Claims 6, 10, 11, 13 and 15 are objected to because of the use of "Sequence Nos.". Use of "SEQ ID NO:" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5-11, 13, 15-17, 20, 21, 24, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-11, 13, 15-17, 20, 21, 24, 26 and 27 are directed to a method of synthesizing a heterologous polypeptide utilizing a polynucleotide that is made up of one or more base

sequences having an RNA higher-order structure, wherein at least PK (peudoknot) I, II and III structures and a function for promoting a translation activity are maintained, and wherein the RNA higher-order structure can be a base sequence comprising SEQ ID NO:1-6 or 7, a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been mutated and has a function for promoting a translation activity (claims 5-9, 13, 15-17, 20, 21, 24, 26 and 27); or a method of initiating synthesis arbitrary polypeptide from arbitrary codon comprising the step of changing a combination of base pairs that make up of PK I, II and III in a RNA higher order structure (claims 10 and 11). While the specification indicates that the invention provides an RNA higher-order structure with promoting a translation activity and including a base sequence comprising SEQ ID NO:1-6 or 7, a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been mutated and has a function for promoting a translation activity; and a method of synthesizing a heterologous polypeptide utilizing a polynucleotide having an RNA higher-order structure, wherein the synthesis is carried out in a cell-free protein synthesis system (pages 3-4), the specification does not disclose a genus of variants for an RNA higher-order structure with PK (peudoknot) I, II and III structures and a function for promoting a translation activity, or an RNA higher-order structure is made up of a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to

the base sequence under stringent condition, or a base sequence that has been mutated or altered in the claimed method.

The specification discloses the RNA higher-order structure having a function of promoting translation activity contains a base sequence of SEQ ID NO:1-7 (pages 6-7); the RNA higher-order structure containing three pseudoknot structures (PK I, II and III) contributes to the initiation and acceleration of translation of a protein (e.g., luciferase) *in vitro* and the mutation of PK I in the PSIV-IRES permits translation of a GFP gene, where in vitro translation was carried out using a rabbit reticulocyte lysate (Example 1; Figs. 7 and 8); and utilizing the mutated PSIV-IRES permitted translating a heterologous protein that begins with an arbitrary amino acid in cell-free system using a wheat germ extract (Example 2, Fig. 9). However, the specification does not describe a genus of variants for an RNA higher-order structure with PK (peudoknot) I, II and III structures and a function for promoting a translation activity, or an RNA higher-order structure is made up of a base sequence having at least about 50% of homology to the sequence of SEQ ID NO:1-6 or 7, a complementary strand of the base sequence, a sequence hybridizing to the base sequence under stringent condition, or a base sequence that has been mutated or altered in the claimed method. A description of a specific higher-order RNA structure having a base sequence of SEQ ID NO:1-7 and a specific mutation in the in the PK I of PSIV-IRES does not provide original descriptive support for a genus of variants for an RNA higher-order structure in the claimed method. The disclosure of these base sequences of RNA higher-order structure and specific mutations in the PKI region of the base sequence does not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision all the contemplated nucleotide sequences for an RNA higher-order structure with PK (peudoknot) I, II and III structures and a function for promoting a translation activity. The detailed sequences of RNA higher-order structure must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 5-11, 13, 15-17 and 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 5-11, 13 and 15-17 are indefinite because the claim lacks essential steps in the method of synthesizing a heterologous polypeptide. The missing steps are the system for protein expression (e.g., in vitro) and the translation step. Claims 6-9, 11, 13 and 15-17 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

11. Claims 6, 10, 11, 13, 15 and 21 are indefinite because of the use of the term "a base sequence hybridizing with the base sequences of 1) to 4) under stringent conditions". The cited term renders the claim indefinite, it is not clear under what condition the nucleotide sequence is hybridizing with the base sequence, and what nucleotide sequence the hybridized nucleotide has. Claim 11, 13 and 15 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

12. Claims 10 and 11 indefinite as to "the sequence including a base sequence", it is not clear which sequence "the sequence" refers to. Claim 11 is included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which it depends.

13. Claims 20-25 are indefinite as to what protein expression system is provided for synthesizing a heterologous polypeptide. Claims 21-25 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

14. Claim 25 recites the limitation "except that positions 187-188 of the base sequence of SEQ ID NO:1 are cc instead of uu and positions 158-159 are gg instead of aa" in lines 3-4. There is insufficient antecedent basis for this limitation in claim 22, claim 22 does not recite a mutation in the base sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 5-7, 9 13, 15, 16, 20-23 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sasaki *et al.* (J. Virology, 73, 1219-1226 (1999)).

Sasaki *et al* teach AUG-unrelated translation initiation is mediated by the internal ribosome entry site (IRES) of an insect picorna-like virus (i.e., *Plautia stali* intestine virus (PSIV)) *in vitro*, where the positive-strand RNA genome of the virus contains two non-overlapping open reading frames (ORFs), and the capsid protein gene is located in the 3'-proximal ORF and lacks an AUG initiation codon (Fig. 1); the capsid protein gene was translated cap independently in the presence of the upstream cistron, indicating that the capsid protein is translated by internal ribosome entry; (pages 1220-1221; Figs 2 and 3). The reference also

teaches a LUC (luciferase) gene was used as the second cistron, and in the CAT-IRES-LUC series of constructs, LUC genes without an AUG initiation codon was ligated to the PSIV sequences (Fig. 5; claims 9, 15, 16), and the LUC gene was efficiently translated when fused down stream of nt 6201 (pCAT-$IRES_{6201}$-LUC) and nt 6264 (pCAT-$IRES_{6264}$-LUC) in vitro (pages 1221-1222; Figs. 5 and 7; claims 5, 7, 20, 26), where the $IRES_{6264}$ contains SEQ ID NO:1 (nt 6005-6204, 200 nucleotides; claims 6, 13, 21, 22 and 23). Although the reference does not specifically indicate the $IRES_{6201}$ or $IRES_{6264}$ sequence of PSIV has an RNA higher-order structure (PK I, II or III), the $IRES_{6264}$ sequence contains SEQ ID NO:1 (or $IRES_{6201}$ sequence has at least 50 % homology to SEQ ID NO:1) and has the function of promoting translation activity, thus it would be expected that the IRES sequence has at least PK I, II or III structure, thus the reference anticipates the claimed invention.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
January 21, 2005